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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,201	01/14/2004	Ralf Rosskamp	USAV2003/0012 US NP	3559

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ROSS J. OEHLER
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
KHANNA, HEMANT	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/24/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com
andrea.ryan@sanofi-aventis.com

Office Action Summary	Application No.	Applicant(s)	
	10/757,201	ROSSKAMP ET AL.	
	Examiner	Art Unit	
	Hemant Khanna	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *8-14 and 34-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 15-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/29/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of claims 1-7, 15-33 that belong to Group I in the reply filed on March 03, 2007 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-58 are pending.

Claims 8-14, 34-58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in the reply filed on March 03, 2007.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has filed an application data sheet to claim the benefit of a prior-filed application under 35 U.S.C. 119(e).

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It was not executed in accordance with either 37 CFR 1.66 or 1.68. The signature of Ralf Rosskamp has not been set forth.

Drawings

4. The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. Applicant is required to furnish a drawing under 37 CFR 1.81(c). No new matter may be introduced in the required drawing. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d).

Specification

5. The disclosure is objected to because of the following informalities: presence of blank pages on page 18 and page 24 of the specification.

Appropriate correction is required.

6. The disclosure is objected to because of the following informalities: the title "Brief Description of Drawings" and a listing of all figures by number and corresponding statement explaining what each figure depicts is missing. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 22-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 22-33 are drawn to methods of treating dyslipidemia or atherosclerosis in a pre-diabetic or diabetic Type II population comprising the administration of insulin glargine. Claims 22-33, fail to meet the requirement for an adequate written description of the claimed invention as required by 35 USC 112, first paragraph. There is no reduction to practice of the claimed invention. Other than treating patients having IGT or early Type II diabetes, no figures indicate, that the invention was set forth by the Applicant. For treatment of dyslipidemic patients, no figures indicate a reduction in lipids, while figures indicate modulation of blood glucose in a pre-diabetic population. For treatment of atherosclerosis, the results from the proposed clinical studies are expected.

MPEP 2161.01 (II)(i) states that for each claim drawn to a single embodiment or species, A) determine whether the application describes an actual reduction to practice of the claimed invention, B) if the application does not describe an actual reduction to practice, determine whether the invention is complete as evidenced by a reduction to drawings or structural chemical formulas.

In the absence of further identifying characteristics, one of ordinary skill in the art would not have accepted that Applicant was in possession of the method for treatment of dyslipidemia or atherosclerosis.

9. Claims 1-7, 15-21, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Nature of the invention. The instant invention is to the treatment of IGT or early Type II diabetes in a patient, wherein the patient has a history of serious cardiovascular events or has one or more significant cardiovascular risk factors comprising the administering of an effective dosage of insulin glargine.

Breadth of the claims. According to the language of the claims, the use of insulin glargine as a long lasting insulin as claimed can be extrapolated to the prevention of diabetes Type II by treating IGT or early Type II diabetes in any mammal to any degree.

State and un/predictability of the prior art. The claimed subject matter is lacking in predictability wherein it would at best have invariable results regarding the treatment of IGT or early Type II diabetes at all times. At the time of the invention was made, the successful treatment of IGT, was obtainable by those skilled in the art by lifestyle intervention or pharmacological therapy using metformin, although the effectiveness using metformin was about half that achieved with lifestyle modification (Medscape, page 6). Further, substantially greater benefit was seen in a subset of younger and obese individuals. It is presumed that the Applicant's intent is to prevent diabetes II by treating a risk factor for diabetes, namely IGT. Since the success of the former reads on not only predicting that IGT or early Type II diabetes precedes diabetes II at all times but being able to accurately define the natural history of IGT in a patient, the treatment

of IGT is not enabled in view of contemporary knowledge in the art. The former is reflected by the findings in two published manuscripts.

Costa teaches that as of 2002, "the main reason to identify and treat IGT is to prevent or delay the onset of Type II diabetes mellitus (abstract). Further, Costa teaches that "Several longitudinal studies have provided the information needed to define IGT, which is not a disease entity and is considered to be a temporary condition between normality and diabetes mellitus (Definition and Diagnosis, page 205).

Medscape teach that as of 2007, "A more difficult issue is whether drug therapy is warranted to delay/prevent diabetes in individuals with IFG/IGT. Although several drugs successfully slowed progression to diabetes, there are many issues that need to be considered before medications can be recommended" (Medscape, page 6). Further, Medscape teaches "The transition from the early metabolic abnormalities that precede diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes may take many years" (Medscape, page 1). Further Medscape teaches "The natural history of both IFG and IGT is variable, with 25% progressing to diabetes, 50% remaining in their abnormal glycemic state, and 25% reverting to NGT over an observational period of 3-5 years" (Medscape, page 2).

The poor accuracy of reproducing the natural history of IFG is also taught by Medscape. Medscape teaches "Also, the poor precision and accuracy of glucose measurements and the poor reproducibility of the glucose tolerance test itself contribute to the difficulty of defining the natural history of IFG/IGT in any one individual" (Medscape, page 2).

Taken together, Medscape teaches "None of the completed studies allow us to determine definitely whether the interventions "reset the clock" or altered the rate of progression" (Medscape, page 4).

Working examples. The Applicant has provided the results from only one study wherein insulin glargine is administered to a combined patient population comprising distinct populations of IGT, IFG, Type II diabetes, and NGT. Moreover, in the above study the Applicant has only chosen one screen (blood glucose) to identify the efficacy of administration of insulin glargine, without disclosing the individual contribution of the IGT population or an early Type II population to the combined effect seen in the screen. Additionally, the Figure shows no statistical difference in the change from endpoint to baseline at time points 8 hrs to 24 hrs when insulin glargine is administered versus placebo.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods to extrapolate to means of treating IGT or early Type II diabetes in a patient specific population with an effective dosage of insulin glargine. There is lack of predictability in the art regarding the treatment of IGT or early Type II diabetes as a means to prevent diabetes by the administration of insulin glargine. The specification does not explicitly describe a treatment endpoint in patients predicted to be afflicted with diabetes II as a result of having IGT.

Amount of experimentation necessary. Given the unpredictability of the art in view of treatment of IGT, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the

invention commensurate with the scope of the claims. Although the Applicant's have identified an interesting use of administering insulin glargine, but essentially all of the work required to develop a treatment method for IGT or early Type II diabetes has been left for the others.

Relative Skill of those skilled in the art. In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a Ph.D. or M.D. with several years of experience in the art. As the cited art would point to, even with a level of skill in the art that is Ph.D. or M.D. predictability of the results is not invariable.

In consideration of each of the factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

10. Claims 22-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Nature of the invention. The instant invention is to the treatment of diabetic dyslipidemia or atherosclerosis in a patient diagnosed with IFG or Type II diabetes comprising the administering of an effective dosage of insulin glargine.

Breadth of the claims. According to the language of the claims, the use of insulin glargine as a long lasting insulin as claimed can be extrapolated to treat risk factors for cardiovascular disease (CVD), such as dyslipidemia and atherosclerosis in a patient population selected from IFG or Type II diabetes to any degree.

State and un/predictability of the prior art. The claimed subject matter is lacking in predictability wherein it would at best have invariable results regarding the treatment of dyslipidemia or atherosclerosis in a pre-diabetic or diabetic Type II poplulation. At the

time of the invention was made, the successful treatment of atherosclerosis, was obtainable by those skilled in the art by pharmacological therapy using troglitazone and acarbose (Medscape, page 5). It is presumed that the Applicant's intent is to reduce the risk of a CVD event by treating dyslipidemia or atherosclerosis in pre-diabetic populations, such as those having IGT. Since the success of the former reads on predicting that CVD risk factors can be attributed to the development of diabetes Type II, the treatment of dyslipidemia or atherosclerosis is not enabled in view of contemporary knowledge in the art. The former is reflected by the findings in a published manuscript.

Medscape teach that as of 2007, "Even so, it is unclear whether the CVD risk associated with IFG or IGT can be attributed to the development of diabetes during follow-up or whether these states per se convey such risk (page 3). Further Medscape teaches "Since studies to demonstrate the improvements in hard outcomes (e.g., changes in the incidence of micro or macrovascular disease) may not be feasible, future research studying the effect(s) of interventions on the pathophysiology of IFG, IGT, and diabetes might establish important therapeutic targets (page 4).

The dissociation between diabetes delay/prevention and reduction in CVD risk factors is also taught by Medscape (page 5). Medscape teaches "One of the major reasons to recommend therapeutic interventions for individuals with IFG/IGT is the potential to reduce the long-term increased risk of CVD associated with diabetes. The potential for achieving this goal can be assessed by evaluating three distinct outcomes:cardiovascular risk factors, surrogate markers for atherosclerosis, or clinically

significant cardiovascular events. Published trials have not been sufficiently powered to show a reduction in these hard outcomes" (page 5).

Taken together, Medscape teaches "The impact on CVD risk factors or events when pharmacological agents are used to prevent/delay diabetes is even less clear and may differ depending on the medication used" (Medscape, page 5).

Working examples. The Applicant has not provided the results from any studies wherein insulin glargine is administered to a patient population to show efficacy in reducing CV disease. Instead the Applicant proposes the expected results from such studies in the specification. While the ORIGIN study has been undertaken by the Applicant , the specification [0080] states " Wherein it is expected that LANTUS will be shown to be efficacious in reducing CV disease". The specification also states [0081] "Despite the novelty of the treatment paradigm proposed for the ORIGIN study, it is believed that hypoglycemia will be minimal based on several factors". Further, the specification states [0092] "Treatment with long acting insulin, particularly insulin glargine, is expected to safely and effectively retard atherosclerosis progression in patients with IGF, IFG, or Type II diabetes". Further the specification states [0095] "Treatment with long acting insulin, particularly glargine, is expected to prevent an increase in carotid intimal thickness of the extracranial carotid artery".

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods to treat risk factors for CV disease, such as atherosclerosis or dyslipidemia predicted to occur upon the progression of IGT to diabetes Type II. There is lack of predictability in the art regarding the treatment of

treatment of CVD risk factors by pharmacological agents in populations of pre-diabetic and diabetic Type II patients. The specification does not explicitly disclose results from the treatment of patients with CVD risk factors with insulin glargine.

Amount of experimentation necessary. Given the unpredictability of the art in view of treatment of atherosclerosis or dyslipidemia in pre-diabetic or diabetic Type II populations, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate with the scope of the claims. Although the Applicant's have identified an interesting use of administering insulin glargine, but essentially all of the work required to develop a treatment method for dyslipidemia or atherosclerosis has been left for the others.

Relative Skill of those skilled in the art. In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a Ph.D. or M.D. with several years of experience in the art. As the cited art would point to, even with a level of skill in the art that is Ph.D. or M.D. predictability of the results is not invariable.

In consideration of each of the factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hemant Khanna whose telephone number is (571) 272-9045. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hemant Khanna Ph.D.
April 11, 2007

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600